Original research articles

Corresponding author:

Ai Yoneda, Department of Ophthalmology, The Japanese Red Cross Nagasaki Genbaku Hospital, 3-15 Mori-machi Nagasaki 852-8511, Japan

Email: aiyoneda@nagasaki-med.jrc.or.jp

Initial treatment for polypoidal choroidal vasculopathy: Ranibizumab combined with photodynamic therapy or fixed-dosing aflibercept monotherapy

Ai Yoneda,[1, 2] Harumi Wakiyama,[1, 2] Junko Kurihara,[1, 2] Takashi Kitaoka,[2]

[1]Department of Ophthalmology, The Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan

[2]Department of Ophthalmology and Visual Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Abstract

Purpose

To compare the 2-year outcomes of combination therapy using intravitreal ranibizumab (IVR) and photodynamic therapy (PDT) with those of fixed-dosing intravitreal aflibercept (IVA) monotherapy as initial treatment for treatment-naïve polypoidal choroidal vasculopathy (PCV).

Methods

We retrospectively reviewed 63 eyes of 61 patients with treatment-naïve PCV who had undergone at least 24 months of follow-up. Forty-three eyes underwent IVR–PDT combination therapy and 20 eyes underwent fixed-dosing IVA monotherapy. Visual outcomes and the number of treatments were compared between the two groups.

Results

The mean logarithm of minimal angle of resolution best-corrected visual acuity significantly improved from 0.48 ± 0.41 at baseline to 0.30 ± 0.47 at 24 months in the IVR–PDT group ($P = .0002$) and from 0.30 ± 0.18 at baseline to 0.16 ± 0.18 at 24 months in the IVA group ($P = .004$), with no significant intergroup differences. The mean number of IVR or IVA injections over 24 months was 5.7 ± 4.5 in the IVR–PDT group and 12.2 ± 3.8 in the IVA group ($P < .0001$).

Conclusion

The IVR–PDT combination therapy was noninferior to fixed-dosing IVA monotherapy in improving visual acuity and required fewer injections.

Key words

aflibercept, combination therapy, photodynamic therapy, polypoidal choroidal vasculopathy, ranibizumab

Introduction

Polypoidal choroidal vasculopathy (PCV) is characterized by polypoidal lesions and branching vascular networks on indocyanine green angiography (ICGA) [1-3]. Dansingani KK et al showed that PCV was aneurysmal type 1 neovascularization[4]. The persistent exudation and massive hemorrhage associated with PCV can induce severe vision loss[5] [6]. The available treatment strategies for PCV include focal laser therapy, photodynamic therapy (PDT), anti-vascular endothelial growth factor (VEGF) therapy, or a combination of these. Combination therapy with PDT and anti-VEGF administration has shown favorable outcomes[7-27]. The EVEREST II study[26] was a randomized prospective study in which combination therapy with intravitreal ranibizumab (IVR) and PDT was superior to ranibizumab monotherapy in improving the best-corrected visual acuity (BCVA) and ensuring complete polyp regression over 12 months.

Aflibercept is an anti-VEGF agent. Some studies have reported that intravitreal aflibercept (IVA) may improve BCVA and induce regression of polypoidal lesions[28-37]. Maruyama et al[33] reported that fixed-dosing aflibercept treatment showed greater effectiveness than as-needed injections. However, the frequent injections impose a large economic burden on patients. Thus, a treatment protocol that uses fewer injections while maintaining the effectiveness of fixed-dosing regimens may serve as a more cost-effective alternative for patients with PCV.

Therefore, the purpose of this study was to compare the 2-year visual outcomes and the number of treatments between IVR–PDT combination therapy and fixed-dosing IVA monotherapy.

Methods

We retrospectively reviewed 63 eyes of 61 consecutive patients with treatment-naïve PCV. Each patient received initial treatment at The Japanese Red Cross Nagasaki Genbaku Hospital between November 2009 and November 2013. All patients were followed up for at least 24 months. Exclusion criteria were a history of previous treatment for PCV, concurrent ocular diseases affecting visual acuity, or vitrectomy. This retrospective study followed the Declaration of Helsinki and was approved by the institutional review board at The Japanese Red Cross Nagasaki Genbaku Hospital. The institutional review board approved the use of opt-out consent method. The trial was

registered with the University Hospital Medical Information Network (UMIN ID: 000029148).

All patients underwent comprehensive ocular examinations including BCVA assessments with the Landolt C chart, fundus color photography, spectral-domain optical coherence tomography (OCT) with RTVue (Optovue, Inc. Fremont, CA, USA), and fluorescein angiography (FA) and ICGA with F-10 (NIDEK, Gamagori, Japan) at baseline. The diagnosis of PCV was based on the presence of polyp-like lesions with branching vascular networks on ICGA.

The choice of the initial treatment depended on the period when the patients underwent treatment. All patients who started treatment between November 2009 and November 2012 were treated with IVR–PDT combination therapy. Since aflibercept was approved in Japan in September 2012, all patients who started treatment between December 2012 and November 2013 were treated with fixed-dosing IVA monotherapy. Patients in the combination therapy group received one to three consecutive monthly IVR injections (0.5 mg/0.05 ml) and PDT. We had planned for three monthly IVR injections, however some patients received just one or two injections for financial reasons if the exudative changes had disappeared. PDT was performed within 7 days after the initial IVR injection. Verteporfin (6 mg/m^2) was administered for 10 minutes. Fifteen minutes after the start of the injection, a 689-nm laser delivered 50 J/cm^2 of energy for 83 seconds. The laser spot size was determined by adding 1,000 μm to the greatest linear dimension (GLD) of the PCV lesions, including the polyps and branching vascular networks, on ICGA. In contrast, patients in the fixed-dosing IVA monotherapy group were treated with three monthly IVA injections (2.0 mg/0.05 ml) followed by injections every 2 months over 12 months. Rescue IVA injection was administered when the BCVA worsened with exudative changes on OCT during the fixed-dosing period.

Both groups were subsequently followed up every month. All patients underwent BCVA assessments, fundus examinations, and OCT examinations at each visit. Retreatment with IVR or IVA was conducted pro re nata (PRN) when residual or recurrent exudative changes were seen on OCT. The anti-VEGF agent in the IVR–PDT group was switched from ranibizumab to aflibercept during the PRN period after aflibercept was approved in Japan in September 2012. Follow-up FA and ICGA were performed at 3 months after the initial treatment and when physicians determined that it was necessary, such as when refractory exudative changes were seen or OCT findings

suggested recurrence of polyps. Additional PDT was performed when residual or recurrent polyps with subretinal fluid were seen on ICGA.

Statistical analysis was performed using SPSS ver.24.0 for Windows. The BCVA was converted into logarithm of the minimum angle resolution (logMAR) visual acuity values for analysis. The Wilcoxon signed-rank test with Bonferroni correction was used to compare the significance of the difference in BCVA and central retinal thickness (CRT) values between baseline and 3, 6, 12, and 24 months after treatment in each group. The Mann-Whitney *U* test was used to compare the changes in BCVA and CRT from baseline and the numbers of injections between groups. Fisher's exact test was used to analyze categorical variables. The retreatment-free interval was assessed using the Kaplan-Meier method, and two groups were compared using the log-rank test. A probability P value less than 0.05 was considered significant.

Results

Forty-three eyes of 41 patients (32 male, 11 female; average age, 73.3 years) were treated with the IVR–PDT combination therapy, while 20 eyes of 20 patients (15 male, 5 female; average age, 69.3 years) were treated with fixed-dosing IVA monotherapy. The baseline characteristics of the patients are listed in the Table. There were no intergroup differences in the baseline characteristics. The mean follow-up period was 5.5 ± 1.7 years in the IVR–PDT group and 3.9 ± 0.6 years in the fixed-dosing IVA group.

Table. Baseline Characteristics of Patients with Treatment-Naïve Polypoidal Choroidal Vasculopathy

	IVR–PDT (n=43)	IVA (n=20)	*P* value
Sex			
Male/Female	32/11	15/5	1.000[a]
Age, years			
Mean ± SD	73.3 ± 7.6	69.3 ± 7.5	0.053[b]
BCVA, logMAR			
Mean ± SD	0.48 ± 0.41	0.30 ± 0.18	0.065[b]
CRT, μm			
Mean ± SD	394.9 ± 116.9	387.0 ± 96.3	0.793[b]

GLD, μm			
Mean ± SD	4281.5 ± 1312.7	4833.3 ± 2122.2	0.210[b]

IVR = intravitreal ranibizumab, PDT = photodynamic therapy, IVA = intravitreal aflibercept, BCVA = best corrected visual acuity, logMAR = logarithm of the minimal angle of resolution, CRT = central retinal thickness, GLD = greatest linear dimension, SD = standard deviation

[a]Fisher's exact test

[b]Mann–Whitney *U* test

In the IVR–PDT group, the mean ± standard deviation (SD) logMAR BCVAs at baseline and 3, 6, 12, and 24 months after the initial treatment were 0.48 ± 0.41, 0.30 ± 0.30, 0.28 ± 0.30, 0.27 ± 0.35, and 0.30 ± 0.47, respectively. The BCVA improved significantly at 3 ($P < .0001$), 6 ($P < .0001$), 12 ($P < .0001$), and 24 months ($P = .0002$) after treatment. In the fixed-dosing IVA group, the mean ± SD logMAR BCVAs at baseline and 3, 6, 12, and 24 months after the initial treatment were 0.30 ± 0.18, 0.16 ± 0.19, 0.15 ± 0.13, 0.12 ± 0.17, and 0.16 ± 0.18, respectively. The BCVA improved significantly at 3 ($P = .004$), 6 ($P = .008$), 12 ($P = .001$), and 24 months ($P = .004$) after treatment. The mean changes in the logMAR BCVA over 24 months are shown in Figure 1. There were no significant intergroup differences.

[insert Figure 1.]

Figure 1 Mean best-corrected visual acuity in eyes with polypoidal choroidal vasculopathy treated with a combination of intravitreal ranibizumab and photodynamic therapy (IVR–PDT) or intravitreal aflibercept (IVA) monotherapy

*: $P < .05$ compared with the baseline in each group

The mean ± SD CRTs at baseline and 3, 6, 12, and 24 months after the initial treatment were 394 ± 117, 243 ± 49, 250 ± 65, 243 ± 45, and 253 ± 74, respectively, in the IVR–PDT group and 387 ± 96, 267 ± 105, 258 ± 85, 240 ± 41, and 243 ± 56, respectively, in the fixed-dosing IVA group. In comparison with the baseline, the mean CRTs at 3, 6, 12, and 24 months after treatment significantly decreased in both groups (all $P < .0001$; Figure 2). There were no intergroup differences.

[insert Figure 2.]

Figure 2 Mean central retinal thickness in eyes with polypoidal choroidal vasculopathy treated with a combination of intravitreal ranibizumab and photodynamic therapy (IVR–PDT) or intravitreal aflibercept (IVA) monotherapy

*: $P < .05$ compared with the baseline in each group

Twenty of the 43 eyes (46.5%) in the IVR–PDT group and 15 of the 20 eyes (75%) in the fixed-dosing IVA group required retreatment during the 24-month period. The median retreatment-free interval between the initial treatment and the retreatment was 25 months in the IVR–PDT group and 18 months in the fixed-dosing IVA group, with the interval being significantly longer in the IVR–PDT group ($P = .024$; Figure 3). The mean numbers of IVR and/or IVA injections in the first year and the second year were 3.6 ± 2.2 and 2.1 ± 3.6 in the IVR–PDT group and 8.1 ± 0.9 and 4.1 ± 3.1 in the fixed-dosing IVA group, respectively, with the values in the IVR–PDT group being lower in both the first ($P < .0001$) and the second years ($P = .012$). Nine of the 43 eyes (21.0%) in the IVR–PDT group were switched ranibizumab to aflibercept during the PRN period. The mean numbers of IVR and IVA injections for these 9 eyes were 4.6 ± 1.7 and 4.7 ± 3.3, respectively. Six of the 43 eyes (14.0%) in the IVR–PDT group and two of the 20 eyes (10.0%) in the fixed-dosing IVA group received additional PDT. The mean number of PDT sessions over 24 months was 1.1 ± 0.4 in the IVR–PDT group and 0.2 ± 0.5 in the fixed-dosing IVA group.

[insert Figure 3.]

Figure 3 The Kaplan-Meier curve shows the proportion of retreatment-free subjects who received a combination of intravitreal ranibizumab and photodynamic therapy (IVR–PDT) or intravitreal aflibercept (IVA) monotherapy. Time (months) is from the initial treatment to retreatment.

The follow-up FA and ICGA examinations were performed in 39 eyes at 3 months after the initial treatment. Twenty of 28 eyes (71.4%) in the IVR–PDT group and 5 of 11 eyes (45.5%) in the fixed-dosing IVA group showed complete polyp regression.

None of the patients developed systemic complications associated with PDT or intravitreal anti-VEGF injections. Three eyes (7.0%) in the IVR–PDT group and two eyes (10.0%) in the IVA group developed a new subretinal hemorrhage larger than a disc area during the 24-month period. One eye (5.0%) in the IVA group developed a retinal pigment epithelium tear within a month after the initial IVA injection.

Representative cases in the IVR–PDT group and the IVA group are shown in figure 4 and 5, respectively.

[insert Figure 4.]

Figure 4 A 60-year-old man with polypoidal choroidal vasculopathy treated with intravitreal ranibizumab and photodynamic therapy. Baseline indocyanine green angiography (ICGA) shows polypoidal lesion (A). Baseline horizontal optical coherence tomography (OCT) shows subretinal fluid with a polypoidal lesion (B). At 3 months after initial combination therapy, ICGA shows regression of polypoidal lesion (C) and horizontal OCT shows no subretinal fluid (D).

[insert Figure 5.]

Figure 5 A 68-year-old man with polypoidal choroidal vasculopathy treated with intravitreal aflibercept (IVA) monotherapy. Baseline indocyanine green angiography (ICGA) shows polypoidal lesion (A). Baseline horizontal optical coherence tomography (OCT) shows subretinal fluid with pigment epithelial detachment (B). At 3 months after initial IVA injection, ICGA shows no regression of polypoidal lesion (C) and horizontal OCT shows persisting subretinal fluid (D).

Discussion

The present study showed that IVR–PDT combination therapy significantly improved BCVA throughout the 24-month period after the treatment, and its effectiveness in PCV patients was noninferior to that of fixed-dosing IVA monotherapy while requiring fewer injections.

The EVEREST II study[26] was performed as a double-masked, multicenter randomized clinical trial to compare IVR–PDT combination therapy with IVR monotherapy. The results showed that the combination therapy was superior to IVR monotherapy with respect to BCVA (8.3 letters vs. 5.1 letters) and complete polyp regression (69.3% vs. 34.7%) over 12 months. Some reports have described IVR–PDT combination therapy in PCV patients with 2-year follow-up data[16 23-25 27]. Saito et al[16] reported that the combination therapy significantly improved the mean logMAR BCVA from 0.52 at baseline to 0.26 at month 24, whereas PDT monotherapy maintained the

mean logMAR BCVA from 0.58 at baseline to 0.60 at month 24. Sakai et al[24] reported that the combination therapy significantly improved mean logMAR BCVA from 0.47 at baseline to 0.26 at month 36, whereas IVR monotherapy maintained the mean logMAR BCVA from 0.41 at baseline to 0.48 at month 36.

In previous studies, fixed-dosing aflibercept monotherapy showed favorable visual outcomes and polyp regression in patients with PCV[28 29 33 36 37]. Maruyama et al[33] reported that IVA monotherapy was effective in improving or maintaining vision over 3 years in PCV patients. They also compared the fixed-dosing and as-needed regimens, and their results showed that fixed-dose IVA treatment improved mean logMAR BCVA from 0.33 at baseline to 0.13 at month 36, whereas as-needed IVA treatment maintained the mean logMAR BCVA from 0.28 at baseline to 0.23 at month 36.

Our results showed that the IVR–PDT combination therapy improved the mean logMAR BCVA from 0.48 at baseline to 0.27 at month 24 and the fixed-dosing IVA monotherapy also improved the mean logMAR BCVA from 0.30 at baseline to 0.16 at month 24. Complete polyp regression rates at month 3 were 71.4% in the IVR–PDT group and 45.5% in the fixed-dosing IVA group. There were no significant intergroup differences in BCVA changes and complete polyp regression rates. Both combination therapy of IVR and PDT and fixed-dosing IVA monotherapy showed favorable outcomes as well as those reported previously.

The mean number of anti-VEGF injections was significantly fewer in the IVR–PDT group. During the first year, patients in the IVR–PDT group received 1-3 planned IVR injections plus PRN injections, while those in the IVA group received eight planned IVA injections plus rescue injections. Thus, the mean number of injections was significantly fewer in the IVR–PDT group. Although patients in both groups received PRN injections during the second year, the mean number of injections was significantly fewer in the IVR–PDT group. The retreatment-free interval between the initial treatment and the retreatment was significantly longer in the IVR–PDT group. Therefore, the combination therapy may reduce the treatment burden. Three eyes in the IVR–PDT group and two eyes in the IVA group developed a severe subretinal hemorrhage. All of these adverse events occurred during the PRN injection period and at least 4 months after PDT in the IVR–PDT group. Thus, we considered they were not induced by PDT but by the recurrence of PCV.

The limitations of this study include the retrospective study design, the relatively small sample size, the use of two different anti-VEGF in the comparison of the two groups and the use of two different anti-VEGF in the some of the patients of the IVR–PDT group. A randomized prospective study with a larger sample size will be needed to confirm the results of the present study.

In conclusion, the initial IVR–PDT combination was as effective as fixed-dosing IVA monotherapy in improving visual acuity over a 2-year period in patients with PCV. The combination therapy showed these outcomes with fewer anti-VEGF injections and contributed to achieving a longer retreatment-free interval.

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Figure 1

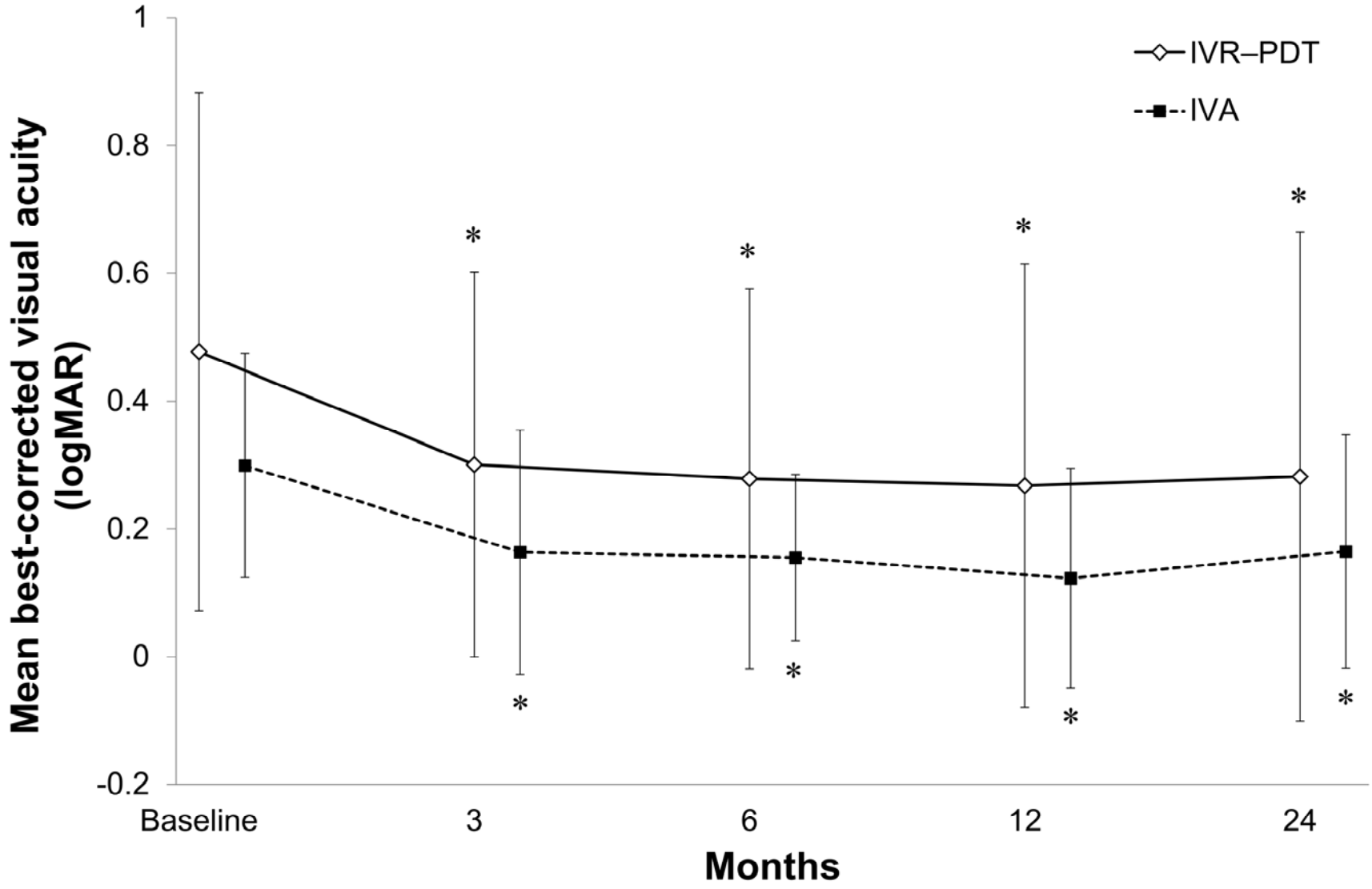
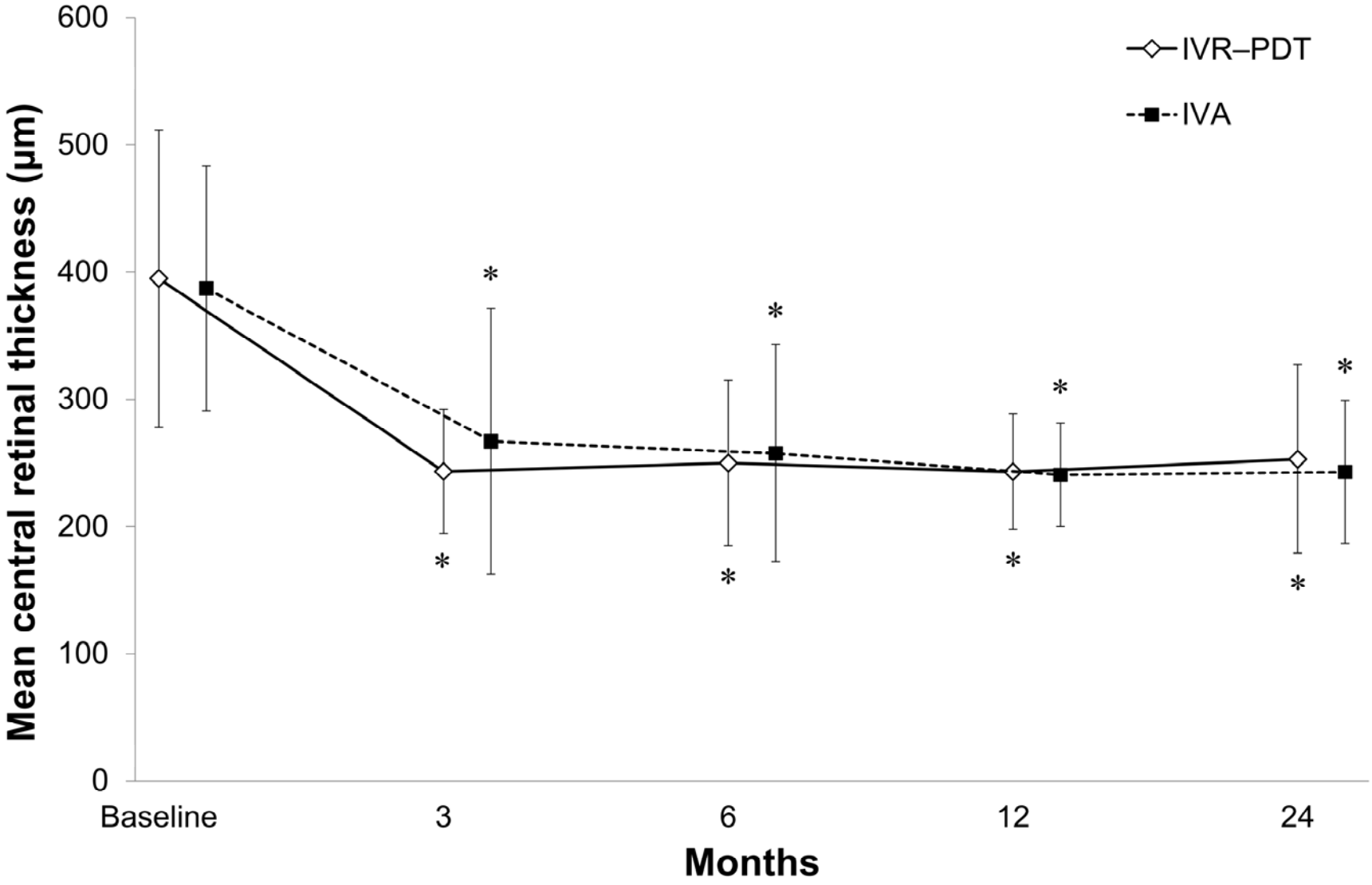

IVR–PDT
IVA
Mean best-corrected visual acuity (logMAR)
1
0.8
0.6
0.4
0.2
0
-0.2
Baseline
3
6
12
24
Months
*

Figure 2


600
500
400
300
200
100
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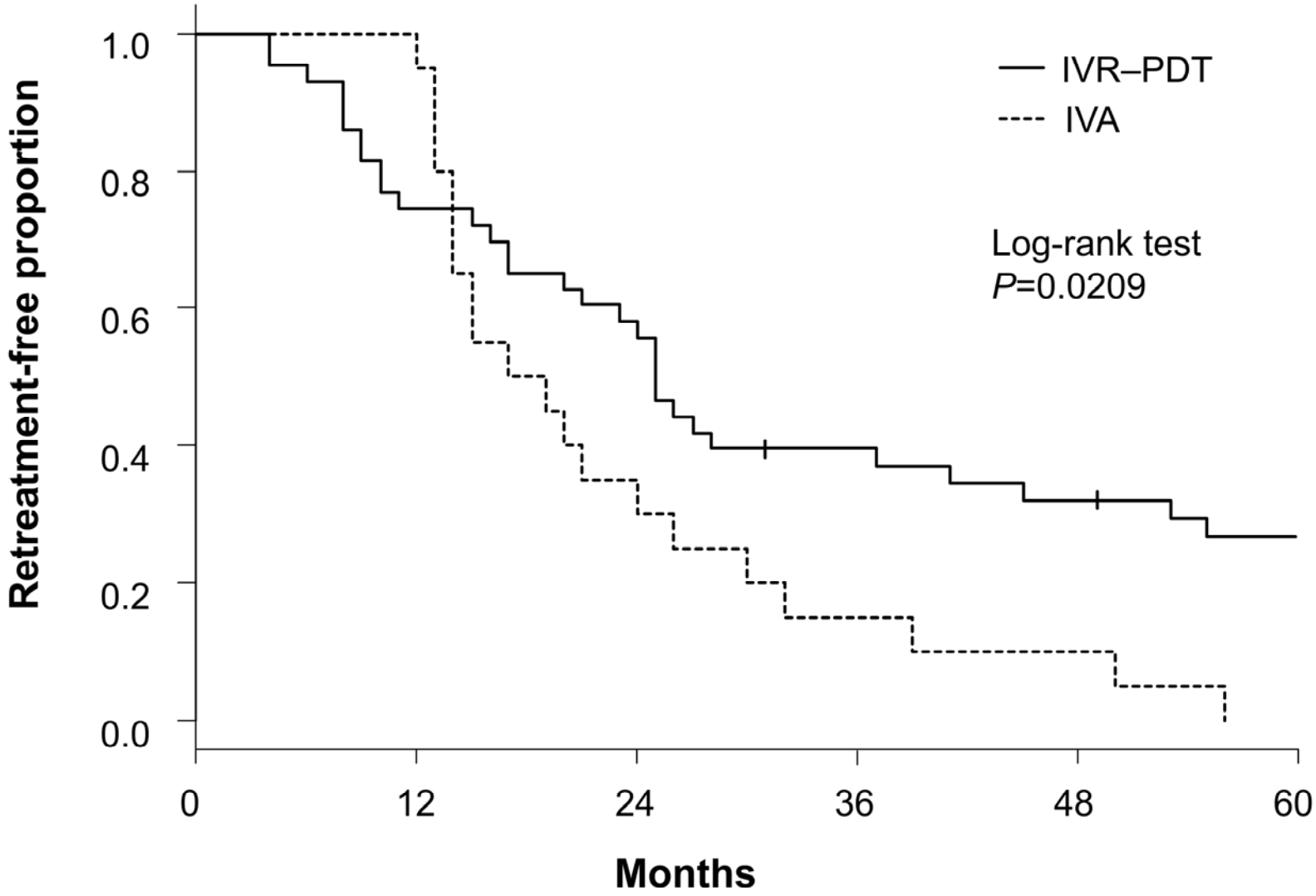
Mean central retinal thickness (μm)
IVR–PDT
IVA
*
Baseline
3
6
12
24
Months

Figure 3


Retreatment-free proportion
1.0
0.8
0.6
0.4
0.2
0.0
0
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24
36
48
60
Months
IVR–PDT
IVA
Log-rank test
P=0.0209

Figure 4

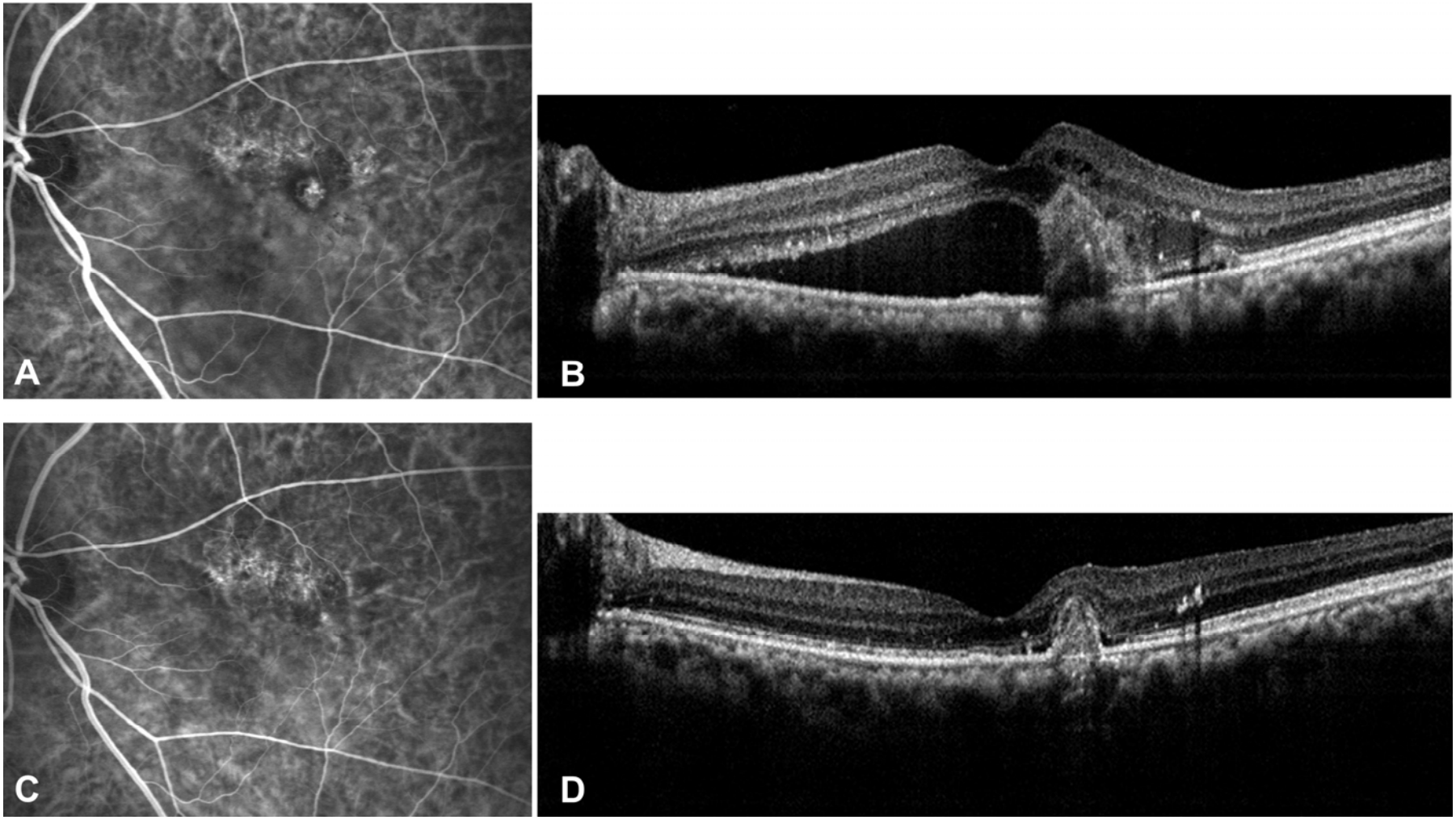

Figure 5